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POSITION PAPER

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Abstract This position paper of the International Osteoporosis Foundation makes recommendations for vitamin D nutrition in elderly men and women from an evidence-based perspective.

Keywords Musculoskeletal health · Requirement · Vitamin D

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This statement has been endorsed by the IOF Committee of Scientific Advisors

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Introduction

Vitamin D is important for bone and muscle development, function, and preservation. The serum 25OHD concentration is the best available clinical indicator of vitamin D status. Until recently, optimal serum 25OHD concentration was considered to be that level associated with maximal parathyroid hormone (PTH) suppression. Estimates of that threshold level have clustered around 32–50 nmol/L (12.8–20 ng/ml) and 68–75 nmol/L (27.2–30 ng/ml), depending upon analytical approach used [1]. In the last decade, however, the evidence base for older men and women has grown to include many randomized, controlled clinical trials (RCTs) with falls and fracture endpoints. Because the RCTs have for the most part been conducted in men and women over the age of 60 to 65 years, our recommendations are directed at this large and growing older segment of the adult population. Our objective is to use available evidence to support recommendations for optimal vitamin D status. We approach this by examining

the efficacy of different vitamin D doses administered and levels of 25OHD achieved in reducing risk of falls and fractures. In this process, it is important to consider other factors that influence serum 25OHD levels and responses to oral vitamin D supplementation.

Determinants of serum 25OHD levels and of the serum 25OHD response to oral vitamin D

Vitamin D intake and effective sun exposure are the major determinants of the serum 25OHD level. Several factors influence the increment in serum 25OHD in response to a given dose of vitamin D_3, including the starting level of 25OHD. At a dose of 2.5 μg (100 IU/d), the mean increment ranges from 2.75 nmol/l (1.1 ng/ml) at low starting 25OHD levels to 1.75 nmol/l (0.7 ng/ml) at higher (near optimal) starting levels [2]. The increment in 25OHD in response to a given dose of vitamin D also varies with body size. It is smaller in subjects with high BMI than in individuals with normal BMI [3, 4]. Other factors affect 25OHD levels but have no known impact on 25OHD responses to supplemental vitamin D. Estrogen use increases measured serum 25OHD levels by increasing levels of vitamin D binding protein [5] but does not alter the serum 25OHD increment achieved with supplementation. Serum 25OHD levels decline with aging, but the serum 25OHD response to a given dose of supplemental vitamin D_3 is not affected by age [6]. Similarly, the dietary calcium intake, within the range usually consumed, does not affect the serum 25OHD response to vitamin D supplementation [7]. (The latter statement should not be confused with the observations that the *calcium* requirement may be dependent upon vitamin D status and that an adequate calcium intake is important for bone health [8].) Finally, serum 25OHD levels vary widely across commonly used assays. Until this problem is addressed by widespread use of standard reference material such as the NIST standards [9] and participation in the DEQAS quality control program (www.deqas.org), assay variability will continue to complicate the process of determining the desired 25OHD level and the impact of a given dose on serum 25OHD levels.

Falls

Vitamin D is thought to act on myocyte vitamin D receptors to exert its effect on muscle tissue. In prospective studies, lower serum 25OHD levels have been associated with decreased grip strength and appendicular muscle mass in older men and women [10, 11] Supplementation with vitamin D has improved lower extremity muscle performance and reduced risk of falling in several high-quality double blind RCTs [12]. These trials have employed doses up to 25 μg (1,000 IU) of vitamin D per day, with and without calcium. Supplementation in amounts of 17.5 to 25 μg/day (700–1,000 IU/day) lowered risk of falling by 20% in older individuals, independent of their calcium intake level. In contrast, supplementation with doses of <17.5 μg/day (<700 IU/day) had no detectable effect on falls. From this meta-analysis of available data, it appears that a mean serum 25OHD level of at least 60 nmol/L (24 ng/ml) is needed for optimal fall risk reduction. Observational studies suggest that there may be benefit to increasing serum 25OHD levels beyond 60 nmol/L (24 ng/ml), but higher levels (and doses) have not been evaluated in RCTs.

Fractures

Vitamin D affects fracture risk through its effects on bone metabolism and on risk of falling. Randomized controlled trials indicate that supplementation with vitamin D reduces rates of bone loss in older women [13]. The impact of supplemental vitamin D on fracture risk has been examined mainly in men and women age 65 and older. A recent meta-analysis revealed that vitamin D in doses in the range of more than 10 through 20 μg/day (>400–800 IU/day) reduced risk of non-vertebral and hip fracture by approximately 20% whereas doses up through 10 μg/day (400 IU/day) had no evident effect [14]. Doses above 20 μg/day (800 IU/day) have not been studied. The mean serum 25OHD level associated with reduction in non-vertebral fracture risk was 66 nmol/L (26.4 ng/ml). Hip fracture risk reduction was observed at a mean 25OHD level of 74 nmol/L (29.6 ng/ml) and higher. Based on this

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and other evidence, eight of ten IOF Working Group members felt that 75 nmol/L (30 ng/ml) is the appropriate target level of serum 25OHD for older individuals; in contrast, two members felt that the target should be 50 to 75 nmol/l (20 to 30 ng/ml). The estimate of 75 nmol/l (30 ng/ml) is close to the higher cluster of 25OHD levels associated with maximal PTH suppression [1].

Other potential benefits

Vitamin D insufficiency has been implicated as a contributing factor in a growing number of important chronic diseases including type 2 diabetes, cardiovascular disease, selected cancers, and autoimmune diseases as well as infections, and also to increased mortality. RCTs are needed before causal relationships can be determined and optimal 25OHD levels for prevention can be established. The doses and mean serum levels needed to achieve optimal impact on these non-classical outcomes are not clear.

Global vitamin D status

Vitamin D insufficiency, whether defined as 25OHD levels <75 or <50 nmol/L (<30 or <20 ng/ml), is prevalent worldwide [15]. For instance, the prevalence of levels <75 nmol/L (<30 ng/ml) in postmenopausal women has been reported to be approximately 50% in Thailand and Malaysia, 75% in the USA, and 90% in Japan and South Korea. Vitamin D deficiency, defined as a level below 25 nmol/L (10 ng/ml) is very common in the Middle East and South Asia where mean levels range from 10 to 30 nmol/L (4 to 12 ng/ml) [15, 16]. The high prevalence of suboptimal 25OHD levels in older men and women around the world raises the possibility that many falls and fractures can be prevented with vitamin D supplementation.

Vitamin D preparations

Vitamin D is available in two forms, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). Some find that the two forms are equally effective in raising the serum 25OHD level [17] whereas others find that vitamin D_3 gives a larger increment [18]. We generally recommend that vitamin D_3 be used when available. In some parts of the world, active metabolites are available for use in the treatment of osteoporosis. These metabolites are not a substitute for adequate vitamin D intake. Vitamin D is the substrate for 25OHD and the circulating 25OHD level may be important to support the non-renal production of 1,25-dihydroxyvitamin D. Local production of 1,25-dihydroxyvitamin D appears to mediate some of the non-classical effects of vitamin D.

Recommendations

The estimated average vitamin D requirement for older adults to reach a serum 25OHD level of 75 nmol/L (30 ng/ml) is 20 to 25 μg/day (800 to 1,000 IU/day). Considerably higher doses would be needed to ensure that almost all older adults reached 75 nmol/l (30 ng/ml). Efficacy of doses higher than 20 μg/day (800 IU/day) for fractures and 25 μg/day (1,000 IU/day) for falls however have not been evaluated in RCTs. It is therefore premature to recommend higher intakes for all older adults at this time.

The repletion dose will vary among individuals according to their starting level, their BMI, their effective sun exposure, and other unidentified factors. An intake lower than 20 μg/day (800 IU/day) may be adequate for individuals with regular effective sun exposure. Intake may need to be adjusted upward to as much as 50 μg/day (2,000 IU/day) in individuals who are obese, and in those with osteoporosis, limited sun exposure (institutionalized, homebound), and malabsorption, and in non-European populations known to be at high risk for vitamin D deficiency such as those in the Middle East and South Asia, or immigrants from such regions living in Europe. In these and other high-risk individuals, we recommend measuring the serum 25OHD level. The required dose to reach 75 nmol/L can be estimated from the measured level. Each 2.5 μg (100 IU) of added vitamin D will increase the serum 25OHD level by about 2.5 nmol/L (range 1.75–2.75 nmol/L) or 1.0 ng/ml (range 0.7 to 1.1 ng/ml) [2]. Because of the variability in individual 25OHD responses to supplemental vitamin D, however, in high-risk individuals, the serum 25OHD levels should be retested after about 3 months of supplementation to confirm that the target 25OHD level has been reached.

Conflicts of interest None.

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